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Dr. Dr. Jameson:

Final Comment:
Decision to List Environmental Tobacco smoke as a Known Human Carcinogen

Attached are my final comments regarding this matter. My specific comments are directed toward a response to Mr. Repace's concerns about the quality of the data in our 16 Cities Study, which I discussed at the Committee hearings.

Thank you for the opportunity to comment in this important matter.

Sincerely,

Roger A. Jenkins, Ph.D.
Leader
Sampling and Analysis Group
Chemical and Analytical Sciences Division

cc: Dr. Max Eisenberg, CIAR

Comments to National Toxicology Program
Decision to List Environmental Tobacco smoke as a Known Human Carcinogen

Comments on Presentation of Mr. James Repace

by

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Comments on Presentation by Mr. James Repace

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At the NTP deliberations concerning whether to declare environmental tobacco smoke (ETS) a known human carcinogen, Mr. James Repace, during his five minute oration, made some specific comments on the quality of the data from a study for which I was the principal investigator, the so-called 16 Cities Study (1). The findings of the 16 Cities Study formed the basis of my presentation to the Committee. Mr. Repace said, "..... *We can predict pharmacokinetic data from NHANES III and we can analyze studies like Dr. Jenkins.....But when you look at the nicotine data that he reports versus the NHANES nicotine data — that is these tall bars — there is very poor agreement.....The same thing goes for the Covance study or the Corning Hazelton study.....But if you look at the nicotine levels, they are all much lower than the nicotine level that we would calculate from the NHANES study..... I don't find these studies to be hard data at all. I don't think they should be relied upon.*"

Mr. Repace's argument is equivalent to claiming that, when estimates or predictions from a model do not compare well with direct observations, it is the observations which are wrong. This flies in the face of logic, and is akin to a weatherman, having predicted a blizzard, trying to convince a sunbather that the warmth she feels is a figment of her imagination.

Mr. Repace's approach is reported in a manuscript published in Risk Analysis (2). It is based on two models, both of which he has developed. One model seeks to predict air levels of ETS nicotine from standard physical principles. The second seeks to model the metabolism of the inhaled nicotine. He then validates with data from two studies: serum cotinine levels from the NHANES III study (3), and workplace ETS levels from a study conducted by one of his co-authors, Dr. Katherine Hammond (4).

This approach, from which he derives the criticism of our 16 Cities data, has several flaws. I will comment on those associated with the validation of his model. First, the smoke exposure data he used was obtained from stationary area measurements, not direct personal exposure. The fact is that while individuals may live or work in smoking environments, stationary monitors can not take into account changes in smoke exposure resulting from changes in an individual's micro-environment. In these micro-environments, they may be closer to or farther away from various sources of ETS. The fact is that few non-smokers remain in constant ETS concentration environments throughout their day or night. Even when smoking is unrestricted throughout a facility or home, clearly, there will be micro-environments which have higher and lower concentrations of ETS. It seems nearly impossible that individual personal exposure to ETS can be described by long-term area monitoring.

OSHA recognizes that area samples are inadequate for determining personal exposure to potentially hazardous materials in workplaces, and thus mandates personal breathing zone monitoring when at all possible. Area monitoring may overestimate or underestimate actual personal exposure because it fails to account for individual activity patterns. Among some non-smokers, aversion to ETS is a likely driver in controlling exposure when individuals have some freedom of movement in their working or living environment. Why, in the validation of his model, Mr. Repace chose to use the Hammond area monitoring data rather than published personal exposure data, I can only speculate.

A second flaw in Mr. Repace's validation of his model is that he is trying to meld the results of two independent studies, each of which focused on different objectives. This is a classic apples and oranges approach. One study, NHANES III (3), targeted non-smokers who lived and/or worked in smoking or non-

smoking environments spread throughout the country. A subset of subjects provided blood samples on which, among other things, cotinine levels were determined. This is the study from which Mr. Repace obtained the cotinine data for his validation. The study from which Mr. Repace obtained his ETS exposure data was the Hammond et al study described above, which used fixed area monitoring. While this study was conducted in a variety of workplaces in the State of Massachusetts, it could hardly be called national in scope. But more importantly, the "subjects" in the latter study were not the same as those in the NHANES III study. In fact, there were no subjects at all, just sample collection zones in various workplaces. It seems a large leap of faith to assume that subjects in former group would be exposed in the same fashion as the fixed location area samples would determine in the latter study. In addition, the levels reported in the Hammond et al study are themselves subject to debate, since data from passive monitors, which continued to collect ETS nicotine after no one was present, were corrected in such a manner as to indicate no ETS presence beyond the end of the work day. This is in conflict what we know to be the case: that ETS can remain in a room long after the sources are gone, depending on ventilation rate. At least two published articles (5,6) have indicated that the time integrated levels in the Hammond et al study markedly overestimate actual ETS levels due to this correction error.

In summary, Mr. Repace validates his ETS nicotine/body level of cotinine model using data derived from two vastly different situations. The body cotinine portion of his model is validated by comparison with nationally-obtained serum cotinine levels, while the air nicotine level portion of the model is validated from area monitoring in work locations in a single state. While this may appear self-consistent, in fact, the nicotine from which the cotinine is derived comes from personal exposure to ETS, not area monitoring levels. Unless one sits or stands in the same location all of one's work day, area levels are a poor indicator of individual exposure to ETS. In addition, the area monitoring data which Mr. Repace used in his validation may over-report actual concentrations by nearly a factor of 3, according to published reports. And yet Mr. Repace claims that because the 16 Cities Study direct exposure data does not fit that estimated from his model, our direct exposure data must be wrong.

Mr. Repace also testified to the effect that for our data to be correct, one must assume non-linear pharmacokinetics. That is, that non-smokers would have to metabolize nicotine differently than smokers. Admittedly, I am not a pharmacologist, nor is Mr. Repace. However, it seems at least somewhat conceivable that a non-smoker, who is exposed to a few micrograms of nicotine per day, may metabolize nicotine differently than a smoker, who is exposed to a thousand-fold greater level of the material.

We recently had a manuscript accepted for publication (7) in which we examined both salivary cotinine and nicotine personal exposure data obtained from our 16 Cities Study, and entered that data into an existing model which purports to be able to estimate (8) the direct airborne exposure to nicotine, based on blood or saliva levels of cotinine. We concluded in our analysis that the model (as well as the one published by Mr. Repace) is not supported by the data from the 16 Cities Study, which is the largest study of direct personal exposure to ETS (more than 1500 subjects) ever conducted in a single country. A detailed analysis of the comparison between salivary cotinine and direct personal exposure to nicotine revealed that agreement between estimated ETS exposure and actual ETS exposure may be within a factor of two for the most highly exposed subjects. However, for the large majority of the individuals for which data was available, models based on nicotine metabolism in smokers appear to severely overestimate actual ETS nicotine exposure, perhaps by a factor of ten.

In contrast to the opinion of Mr. Repace, I believe that the data in our 16 Cities Study is indeed sound, and consequently, can be relied upon to provide meaningful comparisons between spousal exposure to ETS and background exposure. Those comparisons indicate that actual background correction factors (the so-called

Z Factor) are much greater than those estimated by the EPA in its risk assessment of ETS in lung cancer (9). In addition, estimated never-smoker misclassification rates, reported in our recently accepted publication (7), are much greater than those used by the EPA in it lung cancer risk assessment. Those two factors together suggest that the actual risk to lung cancer from ETS exposure, using the formulas employed by the EPA, is far lower than that estimated by the EPA.

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